19. (Amended) The DNA array substrate according to claim 16, wherein the first region contains the full match probe and the mismatch probes having one mismatch base to the reference nucleic acid.

20. (Amended) The DNA array substrate according to claim 16, wherein the separate regions are arranged on the substrate in order of signal intensity obtainable by reacting with the reference nucleic acid along a direction of a detection.

21. (Amended) The DNA array substrate according to claim 16, wherein a length of the probes is 8 to 30 nucleotides.

22. (Amended) The DNA array substrate according to claim 21, wherein the length of the probes is 12 to 25 nucleotides.

REMARKS

The claims are 1-23, with claims 1 and 16 being independent. Claims 1, 2, 5-9, 11, 14-16, and 19-22 have been amended. Specifically, claim 1 has been amended to better define and clarify the present invention. Support for this amendment may be found throughout the specification and the claims. Claims 2, 5-9, 11, 14-16, and 19-22 have been amended for clarification, reflecting the changes made to claim 1. No new matter has been added. Reconsideration of the claims is expressly requested.

The specification is objected to by the Examiner. Specifically, the Examiner has alleged that the specification contains nucleotide sequences that are not identified by proper SEQ ID NOs.

Applicants have amended the specification to add SEQ ID NOs. Accordingly, withdrawal of this objection is respectfully requested.

Claims 1, 5, 14, 15, 21 and 22 are objected to and claims 1-23 stand rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite.

Applicants have amended the claims to correct the informalities pointed out by the Examiner on pages 2 and 3 of the Office Action and to clarify the present invention. Specifically, Applicants have changed the allegedly indefinite term "normal sequence" to --wild-type sequence--, corrected the spelling and clarified claims 5, 7, 9, 14, 15, 21 and 22. Also, in claims 1 and 16, Applicants have changed "a region of nucleic acid" to --a portion of nucleic acid-- to more clearly distinguish it from the regions on the substrate. Accordingly, the claim objections and the indefiniteness rejections should be withdrawn.

Claims 16, 17, 19 and 23 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by U.S. Patent No. 5,733,729 (Lipshutz). Claims 1, 2, 5-16 and 19-23 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by U.S. Patent No. 6,309,823 B1 (Cronin). Claims 2, 3, 17 and 18 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Cronin in view of U.S. Patent No. 6,309,824 B1 (Drmanac). Claim 18 stands rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Lipshutz in view of Drmanac. These rejections are respectfully traversed.

Prior to addressing the merits of the rejections, Applicants would like to briefly discuss some of the features and advantages of the presently claimed invention. In the present invention, a full match probe (completely complementary to the wild-type sequence) and mismatch probes, which have one or more bases not complementary to the wild-type sequence, are separately placed in accordance with the number of mismatches in different regions on a substrate for hybridization with a nucleic acid. The signals from hybridized probes are not measured individually, but are measured as a total signal from each region to form a regional pattern of signal intensity.

When a reference nucleic acid having the wild-type sequence and a sample nucleic acid are reacted with the substrate, different signal patterns are obtained. Therefore, since the signal, for example luminescence, is not measured for each immobilized probe but rather a pattern of regional signals is determined, simple and rapid identification of base variations in the test sample is achieved at a low cost. Thereby, the presently claimed invention dispenses with the need for the precision detection apparatuses such as a confocal microscope (See specification, par. [0007]).

Lipshutz is directed to a computer system for analyzing nucleic acid sequences. This reference, however, does not disclose or suggest the arrangement of probes in regions based on signal intensity on a reaction with a reference nucleic acid. As can be clearly seen in Lipshutz at column 7, line 1, through column 8, line 14, and Figs. 7 and 8, the probe arrangement in this reference is substantially different from the present invention.

Furthermore, Lipshutz teaches a system that has a scanner and a detector such as a confocal microscope, which is pointed out by the Examiner on page 4 of the Office Action. As discussed above, the present invention dispenses with the need for such a scanning apparatus. Clearly, Lipshutz cannot anticipate the present invention.

Cronin is directed to probe arrays and methods for detecting mutations in the genes using such arrays. Cronin, however, teaches determining luminescence at the location of each immobilized probe, which requires a precision detection apparatus.

The Examiner has alleged that Cronin teaches immobilizing by cells or different regions.[1] In connection with this immobilization, Cronin discloses that a cell is a pooled mixture of probes and that the individual probes in the pool are not addressable. Further, Cronin states that a cell is scored as hybridizing to a target sequence if at least one probe occupying the cell comprises a segment exhibiting a perfect complementary sequence to the target sequence (See Cronin, col. 22, lines 6-32). Clearly, this is substantially different from the presently claimed invention in which the probes are grouped into regions based, for example, on the number of mismatches or on the differences in signal intensity on a reaction with the reference nucleic acid. Thus, Cronin cannot anticipate the presently claimed invention or render it unpatentable.

Drmanac cannot supply the missing teachings of Cronin. This reference was cited by the Examiner for the alleged disclosure of fluorescent or chemiluminescent labeling of probe assays. However, even if assumed, arguendo, that Drmanac contains this

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1/ The Examiner has pointed to col. 2, lines 6-18, in Cronin to support this allegation. Applicants believe that the correct citation for this proposition is col. 22, lines 6-18.

alleged teaching, the present invention is still patentable over the combination of Drmanac and Cronin, because Drmanac does not disclose or suggest the presently claimed regional probe arrangement.

Lipshutz, which is discussed above, cannot remedy the deficiencies of Cronin and Drmanac. This reference also fails to disclose or suggest the presently claimed probe arrangement. Therefore, the present invention is patentable over the combination of Cronin, Drmanac and Lipshutz.

In conclusion, the cited references, whether considered separately or in any combination, do not teach or suggest the combination of elements presently claimed. Therefore, Applicants respectfully request that all objections and rejections be withdrawn an the present case be passed to issue.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

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APPENDIX

Application No. 09/942,588
Attorney Docket No. 03500.015717

IN THE SPECIFICATION:

Paragraphs beginning on page 20, line 9, and ending on page 20, line 24, have been amended as follows:

That is, the designed nucleic acid are 18-mer nucleic acids harboring variegated above mentioned six bases sandwiched between the common sequences, represented by 5'ATGAACNNGAGNCCCATC3' (SEQ ID NO: 68) where N corresponds to any of 4 bases, A, G, C and T. Actual probes to detect the above sequence should be have a complementary sequence of 5'GATGGGNCTCNNGTTCAT3' (SEQ ID NO: 69).

FIG. 2 shows an arrangement of 64 types of DNA probes on a substrate. A sequence 5' ATGAACCGGAGGCCCATC3' (SEQ ID NO: 65) corresponding to the normal gene is expected to form a hybrid with DNA of probe 42 of 5'GATGGGCCTCCGGTTCAT3' (SEQ ID NO: 42) positioned at the third from the right and the third from the top.

The paragraph beginning on page 23, line 22, and ending on page 23, line 23, has been amended as follows:

No. 65: 5'-Rho-ATGAACCGGAGGCCCATC-3' (SEQ ID NO: 65)

-Reaction condition of hybridization

IN THE CLAIMS:

Claims 1, 2, 5-9, 11, 14-16, and 19-22 have been amended as follows:

1. (Amended) A method for screening of the presence or absence of variation in a portion [region] of a nucleic acid comprising the steps of:

(a) preparing a test nucleic acid corresponding to the portion [region];

(b) preparing a full match probe having a base sequence fully complementary to a wild-type [normal] sequence of the portion [region], and a plurality of mismatch probes [each] having a [at least one] base sequence not complementary to the wild-type [normal] sequence;

(c) fixing the full match and mismatch probes separately to form a plurality of [in separate] regions in accordance with a number of mismatches on a surface of a substrate to prepare a DNA array substrate;

(d) reacting the test nucleic acid with the probes on the DNA array substrate;

(e) measuring a signal intensity of [signals in] each region as a total of [totaly where the] signals originating [are originated] from respective hybrids formed between the test nucleic acid and [one of] the probes to obtain a histogram pattern of signal intensity of the regions; and

(f) determining the presence or absence of mutation in the test nucleic acid comparing with the [a] histogram pattern with a histogram pattern [of signals of all regions] obtained using an array substrate obtained by the step (b) and a reference nucleic acid having the wild-type sequence [a normal sample without variation].

2. (Amended) The method according to claim 1, wherein the signal is a light [emitted from each hybrid] and [the total signal is measured as] a total light quantity emitted from each region is measured as the signal intensity.

5. (Amended) The method according to claim 1, wherein the steps (c) to (f) [(e)] further comprise [are]:

(c) preparing separated regions on a substrate by fixing probes on a surface of the substrate, wherein the separate regions comprise [comprises]:

a first region containing probes which provide a signal of a certain intensity on reaction with a nucleic acid having the wild-type [normal] sequence,

a second region containing probes which provide weaker signals on reaction with the reference [a] nucleic acid [having normal sequence], and

the third region containing probes which do not form hybrids on reaction with the reference [a] nucleic acid [having normal sequence];

(d) reacting the DNA array of the step (c) with the reference [a] nucleic acid [having normal sequence] and measuring a signal of at least one region selected from the three regions to obtain a first pattern; [and]

(e) reacting the DNA array of the step (c) with the test nucleic acid, and measuring a signal [signals] of at least one region [corresponding to the] selected in [region of] the step (d) to obtain a second pattern; and

(f) [(e)] determining the presence or absence of variation in the test nucleic acid by comparing the first and second patterns.

6. (Amended) The method according to claim 5, wherein the selected region is the first region giving a strongest total signal and/or the third region giving no or a weakest signal on reaction with the reference [a] nucleic acid [having normal sequence].

7. (Amended) The method according to claim 5, wherein the separate regions are arranged on the substrate in order of signal intensity [obtainable by reacting a nucleic acid having normal sequence, from the highest intensity to the lowest intensity] along a direction of a detection, wherein the signal intensity is obtainable on a reaction with the reference nucleic acid.

8. (Amended) The method according to claim 5, wherein the selected region is the third region, and [when a total signal is detected with] the test nucleic acid [in the step (d), variation is called positive, and the test nucleic acid] is determined to have variation when the signal is detected in the third region with the test nucleic acid in the step (e).

9. (Amended) The method according to claim 5, wherein the first region contains probes consisting of the full match [a] probe and the mismatch probes [having a fully complementary sequence to the normal sequence and probes] having a one-base mismatch to the wild-type base [normal] sequence. [When reacting with a normal base sequence of a nucleic acid].

11. (Amended) The method according to claim 5, wherein all three are [the] selected [regions are all of the region,] and [determined] the presence or [of] absence of variation is determined by comparing the histogram pattern of signal intensity.

14. (Amended) The method according to claim 1, wherein a base length of the probes is 8 [mer] to 30 [mer] nucleotides.

15. (Amended) The method according to claim 14, wherein the base length of the probes is 12 [mer] to 25 [mer] nucleotides.

16. (Amended) A DNA array substrate for screening a variation in a portion [region] of a nucleic acid[, wherein] comprising:

a full match probe fully complementary to a wild-type [normal] sequence of the portion [region], and a plurality of mismatch probes having at least one base mismatch to the wild-type sequence [are] arranged on the substrate, [; and]

wherein the probes are arranged to form at least two separate regions selected from:

a first region containing at least one probe which provides a signal of a certain intensity on reaction with a reference nucleic acid having the wild-type [normal] sequence,

a second region containing at least one probe which provides a weaker signal than the probe of the first region on reaction with the reference [a] nucleic acid [having normal sequence], and

the third region containing at least one probe which provides no signal on reaction with the reference [a] nucleic acid [having normal sequence].

19. (Amended) The DNA array substrate according to claim 16, wherein the first region contains the full match probe and the mismatch probes having one mismatch base[. When reacting with a normal base sequence of a] to the reference nucleic acid.

20. (Amended) The DNA array substrate according to claim 16, wherein the separate regions are arranged on the substrate in order of [total] signal intensity obtainable by reacting with the reference [a] nucleic acid [having normal sequence, from a highest intensity to a lowest intensity] along a direction of a detection.

21. (Amended) The DNA array substrate according to claim 16, wherein a length of the probes is 8 [mer] to 30 [mer] nucleotides.

22. (Amended) The DNA array substrate according to claim 21, wherein the length of the probes is 12 [mer] to 25 [mer] nucleotides.